

REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application are respectfully requested.

The disclosure was objected to because of an informality, a blank space defined by "[]" at page 24, line 11. This informality has been deleted from the specification. Withdrawal of this objection is thus believed to be in order.

Claim 24 has been rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled by the specification. This rejection is believed to be rendered moot by the enclosed Deposit Declaration.

Enclosed herewith is a Deposit Declaration signed and dated by Yves Denouel. This Declaration shows that the hybridoma 7C4 was deposited under the Budapest Treaty as I-2536. This hybridoma I-2536 (or 7C4) produces monoclonal antibodies 7C4.10 (see point 4 of the deposit declaration by Y. Denouel. Monoclonal antibodies 7C4.10 are exemplified in the specification as No. 7 of Table II at page 14 of the specification. Thus, a hybridoma which produces a monoclonal antibody according to the instant invention has been deposited. This deposit satisfies the requirements of §112.

Withdrawal of the rejection of claim 24 under §112 is thus respectfully requested and believed to be in order.

Claims 17-19, 22, 24, 25-29, 30, 31, 33-35 and 37 have been rejected under §112, first paragraph, as allegedly not being described in the specification. This rejection is believed to be rendered moot by the instant amendment.

Claim 17 has been amended to recite:

17. Monoclonal antibodies or their Fv, Fab, and F(ab')₂ fragments, which recognize an epitope of a bacterium of the species *T. equigenitalis*, and which do not exhibit a crossed reaction with at least *K pneumoniae*, *Ps fluorescens*, *St aureus*, *Str equi*, *P haemolytica*, *P multocida*, *Ps aeruginosa* and *Act equuli*.

Claim 17 has thus been amended to recite "at least *K pneumoniae*, *Ps fluorescens*, *St aureus*, *Str equi*, *P haemolytica*, *P multocida*, *Ps aeruginosa* and *Act equuli*." Support for this amendment may be found in Table II, page 14 of the specification. As shown there, the monoclonal antibodies of applicants' invention do not exhibit a cross reaction with any of these bacteria. The scope of the claims is thus now directed to the monoclonal antibodies that do not bind to the eight bacteria exemplified in the specification.

One skilled in the art could readily identify the monoclonal antibodies of the claims, which do not exhibit a cross reaction with the specified bacteria, as shown in Example 2 of the specification.

Withdrawal of the rejection of record is respectfully requested and believed to be in order.

Claims 17, 19, 26 and 28 have been rejected under §102(b) over Friedrich. This rejection is respectfully traversed.

It is noted that only one page of the Friedrich article was provided to applicants and cited in the rejection. This is believed to be in error. A complete translation of the reference is necessary for the instant rejection to be proper. *See, Ex Parte Gavin*, 62 USPQ2d 1680 (BPAI 2002).

Further, enclosed herewith is an English translation of the "results" obtained by Friedrich. As shown in these results, all the monoclonal antibodies of the reference exhibit a cross reaction with *other* bacteria such as *Streptococcus zooepidemicus* and *Streptococcus equi* (see, page 19). There is nothing in the reference to show whether the reaction is a specific or non-specific. These monoclonal antibodies thus do not fall within the scope of applicants' claims.

Moreover between the eight monoclonal antibodies characterized in the reference, two monoclonal antibodies fail to detect two strains of *Taylorella equigenitalis*: strain I/3 is not detected by monoclonal antibody TF III 11E5 and strain BW 26 is not detected by monoclonal antibody TF I 10D5 (see, page 19). The author notes that between all monoclonal antibodies which were partially characterized, only three showed a good fluorescence: TF II 8D4, TF II 11B5 and TF III 11ES (see, page 20). Monoclonal antibody TF III 11 E5 was eliminated by the author himself because of the non reactivity with the strain I/3 of *Taylorella equigenitalis* (conclusions p 34). Monoclonal antibody TF II 8D4 was the only monoclonal antibody which did not show any reaction in immunoblot with a specific protein of *Taylorella equigenitalis* (see, page 18).

In view of these results, the author imagines two hypotheses:

- (1) "this monoclonal antibody detects a discontinuous epitope, i.e. an epitope on the cell membrane surface, which loses its antigenic properties after denaturing treatment of the bacterial cells with SDS due to the destruction of the tertiary structure".
- (2) "this antibody is directed against lipopolysaccharides (LPS) which are strongly represented in the cell walls of Gram negative bacteria".

However, both hypothesis of the authors are false. First, the treatment with SDS only do not denature the proteins because both conformation and biological activity remain intact. The denaturation is under reducing conditions (treatment with β -mercaptoethanol and high temperature) which cause some conformational changes and epitope destruction. Second, the monoclonals directed against LPS react very well in immunoblot, as shown in Table III of the instant application. Note that monoclonal antibodies 7B7.10 (No. 5) and 7D7.3 (No. 8) of the invention reacted in immunoblot with LPS (22 kDa) protein.

The remaining monoclonal antibody TF II 11B5 of Friedrich reacts with two different proteins 70 KDa and 117 kDa. Such an antibody is not a monoclonal antibody.

By contrast, the instant inventors indeed characterize a monoclonal antibody (7B7.7) which reacted positively with two proteins (34.4 and 40 kDa). After further study, they found that the 7B7.7 hybridoma cells were obtained from a well with two physically separated clones.

Moreover, the monoclonal antibodies partially characterized by Friedrich are directed against other proteins of *Tylorella equigenitalis* than the proteins detected by their monoclonal antibodies. Friedrich's monoclonal antibodies are directed against proteins of 13, 56, 70 + 117, 35, 22 (not LPS), 47 + 70 and 47 kDa. By contrast, the monoclonal antibodies of the instant invention are directed against 150, 120, 52.7, and 22 (LPS) kDa.

Friedrich thus fails to anticipate applicants' claimed invention. Withdrawal of this rejection of record is respectfully requested. Such action is believed to be in order.

Claims 26-28 and 31 were rejected under 35 U.S.C. 102(b) as being anticipated by Akuzawa et al. This rejection is respectfully traversed.

Contrary to the assertion made in Paper No. 7, it is Applicants' opinion that the monoclonal antibodies NA-1 did not react with the antigens used in immunization of "external cell membranes of *T. equigenitalis*." Surprisingly, it "exhibited a strong reactivity in the 28-44 kDa range". In spite of that, the author thought that "monoclonal antibody NA-1 is recognizing polysaccharides or LPS components in the outer membrane". This, however, is incoherent. The inventors note that the 28-44 kDa range is very large for characterization of a protein and that the LPS of *T. equigenitalis* has a molecular weight of 22 kDa. So, the monoclonal antibody NA-1 is not specific for all strains of *T. equigenitalis* and the protein of its reactivity was not identified.

Further, the NA-1 monoclonal antibody reacted with half (5 out of 10) of the strains of wild *T. equigenitalis*. This antibody thus is not specific for all strains of *T. equigenitalis*.

Regarding the second monoclonal antibody "NA-2", no information concerning this monoclonal antibody could be found in the reference. If the rejection is based upon this monoclonal antibody, additional information is respectfully requested to be provided to substantiate the rejection on this basis.

In view of the above, withdrawal of the rejection of record is respectfully requested and believed to be in order.

Claim 18 has been rejected under §103(a) over Friedrich in view of Sugimoto. This rejection is respectfully traversed.

As set forth *supra*, a *prima facie* case of obviousness has not been made without a complete translation of Friedrich. Moreover, for the reasons set forth *supra*, Friedrich fails to disclose or suggest applicants' claimed invention. Nothing of record establishes that Friedrich teaches a monoclonal antibody to *Taylorella equigenitalis*, as instantly claimed.

The description in Sugimoto of the size of *Taylorella equigenitalis* outer membrane antigens fails to overcome or remedy the deficiencies of Friedrich. The combination of references would not provide the monoclonal antibodies as instantly claimed.

Withdrawal of the rejection is respectfully requested. Such action is believed to be in order.

Claim 18 has been rejected under §103(a) over Friedrich in view of Corbel et al. This rejection is respectfully traversed.

As set forth *supra*, a *prima facie* case of obviousness has not been made without a complete translation of Friedrich. Moreover, for the reasons provided *supra*, Friedrich does not provide monoclonal antibodies specific to *T. equigenitalis*, as instantly claimed. Corbel's teaching of antigens of about 22 (LPS) kDa in combination with Friedrich, does not provide a monoclonal antibody as recited in claim 18. The combination of Friedrich and Corbel thus fails to teach or suggest applicants' claimed invention.

Withdrawal of the rejection is respectfully requested. Such action is believed to be in order.

Claims 17, 19, 22, 24, 26, 28, 29, 31, 35 and 37 have been rejected under §103(a) over Tainturier et al in view of Friedrich and Harlow. This rejection is respectfully traversed.

As set forth *supra*, a *prima facie* case of obviousness has not been made without a complete translation of Friedrich.

Tainturier is cited as teaching antibodies and methods for detecting *Haemophilus equigenitalis* in a biological sample and showing antibodies which reacted only with *Haemophilus equigenitalis*. As acknowledged in the rejection, Tainturier fails to show the use of monoclonal antibodies specific for *Haemophilus equigenitalis* antigen. Friedrich is cited as teaching the production of monoclonal antibodies for *Haemophilus equigenitalis* and their use to obtain specific diagnostic to provide better proof of infection. Harlow is cited as teaching specific means, methods and reagents for production of monoclonal antibodies and methods of using same for obtaining a source of antibodies which evidence increased antigen specificity. It allegedly would have been obvious to modify the method of Tainturier in view of the teaching of Friedrich and Harlow because “Friedrich teaches *H. equigenitalis* monoclonal antibodies provide for better proof of diagnosis of infection when analyzing biological samples and Harlow teaches specific methods steps” to obtain monoclonal antibodies, and their use in immunoassay methods. This rejection, however, is in error.

None of the references, either singly or in combination teaches monoclonal antibodies or their fragments, as specifically claimed. There is no teaching in any of the references of monoclonal antibodies which specifically recognize a *T. equigenitalis* epitope, and do not exhibit a crossed reaction with the bacterium as specified in claim 17, for example. Friedrich, as discussed *supra*, fails to teach a monoclonal antibody which is specific for *T. equigenitalis*. Neither Tainturier nor Harlow teach a monoclonal antibody

specific for *T. equigenitalis*, which do not exhibit a crossed reaction with any of the eight specified bacterium.

In view of the above, withdrawal of this rejection is respectfully requested. Such action is believed to be in order.

Claims 30, 33 and 34 have been rejected under §103(a) over Tainturier et al in view of Friedrich and Harlow and further in view of Foster. This rejection is respectfully traversed.

As set forth *supra*, a *prima facie* case of obviousness has not been made without a complete translation of Friedrich.

As stated *supra*, the combination of Tainturier, Friedrich and Harlow fails to disclose or suggest the claimed monoclonal antibodies or fragments thereof. Foster's teaching of general kits does not overcome or remedy the deficiencies of Tainturier, Friedrich and Harlow in teaching the claimed monoclonal antibodies. The combination thus fails to teach the kits which include applicants' claimed antibodies or fragments there.

Withdrawal of the rejection is thus respectfully requested. Such action is believed to be in order.

Claims 18, 19, 26 and 30 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. This rejection is believed to be moot in view of the instant amendments.

Claim 18 now recites that the antibodies or fragments "recognize *T. equigenitalis* proteins." This claim no longer recites a broad range within a narrow range.

In claim 19, the phrase "required monoclonal antibodies" is objected to. The word "required" has been deleted from the phrase. The recitation of "monoclonal antibodies" now finds antecedent basis in the claim.

In claim 26, the phrase "which may contain *T. equigenitalis*, into contact with an effective quantity of at least one monoclonal antibody or a fragment thereof" has been objected to. What the quantity is effective for allegedly is not defined. It is believed to be clear that the quantity should be an effective amount for "a reaction of the antigen-antibody type," based upon the wording in the claim. It is also asserted to be unclear whether the phrase "fragment thereof" refers to *T. equigenitalis* or the monoclonal antibody. As helpfully suggested by the Examiner, the claim has been amended to instead recite "Fv, Fab or F(ab')₂" to overcome this aspect of the rejection.

Claim 30 is objected to for the phrases "reagents, for carrying out the intended immunologic reaction" and "optionally, reagents for blocking the non-antigen-antibody reactions." According to the Examiner, the broad recitation of the phrase "reagents, for carrying out the intended immunologic reaction" would include reagents for blocking non-antigen-antibody reactions because the immunological reaction would function specifically without non-specific reactions. This claim has been amended to recite that the reagents are for "detecting" the intended immunologic reaction. We note that the specification defines the first set of reagents as being those for detecting the intended immunologic reaction. *See*, page 7 of English translation. The optional reagents are thus now distinct.

Withdrawal of this rejection is thus respectfully requested and believed to be in order.

Claims 17 and 30 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled by the specification. This rejection is believed to be moot in view of the instant amendments.

It is asserted that, while the specification is enabling for the production of monoclonal antibodies that specifically bind to *T. equigenitalis* and immunogenic compositions that comprise monoclonal antibodies, it does not enable the use of any monoclonal antibody for prevention or treatment of infection and disease caused by *T. equigenitalis*. Claim 17 specifically recites a monoclonal antibody or its fragment that recognizes an epitope of a bacterium of the species *T. equigenitalis*, and which does not exhibit a cross reaction with specified bacterium. The specification enables claims of this scope. The claims are directed to antibodies that specifically bind to *T. equigenitalis*, and do not react with eight other specified bacteria. Such monoclonal antibodies could be made by a person skilled in the art based upon the teachings of the specification. For example, such methods are shown in the Examples, e.g., Examples 1 and 2. These monoclonal antibodies could then be tested in accordance with, e.g., Examples 3 and 4 of the specification. Example 6 illustrates how to make a vaccine in accordance with the instant invention. Based upon all of these teachings, at the very least, one skilled in the art could make and use monoclonal antibodies as recited in claims 17 and 30. These claims are thus enabled by the specification.

Withdrawal of this rejection is respectfully requested. Such action is believed to be in order.

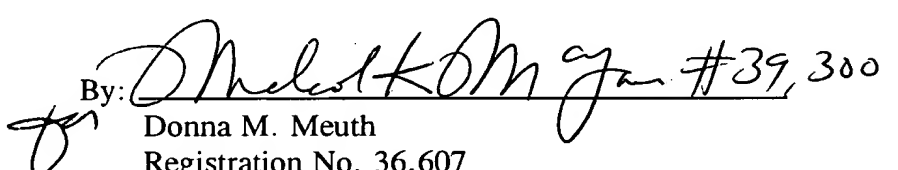
It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (508) 339-3684 so that prosecution of the application may be expedited.

Respectfully submitted,

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Attachment to Reply and Amendment dated July 22, 2002

Marked-up Copy

Page 24, Paragraph Beginning at Line 10

--The purified AcM1 are homopolymerized in the presence of glutaraldehyde at 0.25% for [[]] hours at 4°C. The reaction is stopped by adding a 0.2 M glycine buffer and the polymers are dialysed against PBS.--



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Marked-up Claims 17-19, 22-23, 26, 30 and 35

17. (Twice Amended) Isolated [and purified] monoclonal antibodies or their Fv Fab, and F(ab')₂ fragments, which recognize an epitope of a bacterium of the species *T. equigenitalis*, and which do not exhibit a crossed reaction with [an epitope or epitopes selected from the group consisting of epitopes of a bacterium of a different *Taylorella* species, and epitopes of a bacterium whose genus is different from *Taylorella*] at least *K pneumoniae*, *Ps fluorescens*, *St aureus*, *Str aqui*, *P haemolytica*, *P multocida*, *Ps aeruginosa* and *Act equuli*.

18. (Twice Amended) Isolated [and purified] monoclonal antibodies or their [Fv, Fab, F(ab')₂] fragments, according to claim 17, which [are capable of recognizing] recognize *T. equigenitalis* proteins selected from the group consisting of *T. equigenitalis* proteins of 150 kDa, 120 kDa, 52.7 kDa and 22 (LPS) kDa.

19. (Twice Amended) Isolated [and purified] monoclonal antibodies, which can be obtained from hybridomas by a method comprising:

fusing non-secreting murine myeloma cells with spleen cells from mice immunized against an inactivated strain of the species *T. equigenitalis* or extract(s) of such a strain,

cloning and selecting according to the capacity of [the monoclonal antibodies contained in] their culture supernatant to recognize an epitope or epitopes of a bacterium of

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Marked-up Claims 17-19, 22-23, 26, 30 and 35

the species *T. equigenitalis*, and to not exhibit a crossed reaction with [an epitope or epitopes selected from the group consisting of epitopes of a bacterium of a different *Taylorella* species or epitopes of a bacterium whose genus is different from *Taylorella*] at least *K pneumoniae*, *Ps fluorescens*, *St aureus*, *Str aqui*, *P haemolytica*, *P multocida*, *Ps aeruginosa* and *Act equuli*,

recovering the required monoclonal antibodies, and
optionally purifying said monoclonal antibodies.

22. (Twice Amended) A method of obtaining monoclonal antibodies according to claim 17, comprising:

fusing non-secreting murine myeloma cells with spleen cells from mice immunized [against] by means of a strain of the species *T. equigenitalis* or extract(s) from such a strain,

screening hybridomas whose culture supernatants [contain a monoclonal antibody that exhibits] exhibit a positive reaction with a bacterium of the species *T. equigenitalis* or a fragment thereof, [without exhibiting a crossed reaction with an epitope selected from the group consisting of epitopes of a bacterium of a different *Taylorella* species, and epitopes of a bacterium whose genus is different from *Taylorella*,]

selecting by cloning the hybridomas with respect to their reactivity, in relation to *T. equigenitalis*,

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Marked-up Claims 17-19, 22-23, 26, 30 and 35

recovering the monoclonal antibodies, and
optionally purifying said monoclonal antibodies.

23. (Twice Amended) A method of obtaining monoclonal antibodies according to claim 21, comprising:

fusing non-secreting murine myeloma cells with spleen cells from mice immunized [against] by means of monoclonal antibodies or their Fv, Fab, and F(ab')₂ fragments, which recognize an epitope of a bacterium of the species *T. equigenitalis*, and which do not exhibit a crossed reaction with [an epitope or epitopes selected from the group consisting of epitopes of a bacterium of a different *Taylorella* species, and epitopes of a bacterium whose genus is different from *Taylorella*] at least *K pneumoniae*, *Ps fluorescens*, *St aureus*, *Str aqui*, *P haemolytica*, *P multocida*, *Ps aeruginosa* and *Act equuli*,

screening hybridomas whose culture supernatants [contain a monoclonal antibody that exhibits] exhibit a positive reaction with one of the said monoclonal antibodies or their fragments,

selecting by cloning the hybridomas, and
recovering the required anti-antibodies.

26. (Amended) A method of identification of a bacterium of the species *T. equigenitalis* in a specimen or in a culture comprising:

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Marked-up Claims 17-19, 22-23, 26, 30 and 35

bringing the specimen or the culture to be analyzed, which may contain *T. equigenitalis*, into contact with an effective quantity of at least one monoclonal antibody or Fv, Fab, or F(ab')₂ fragment thereof according to claim 17, under conditions permitting a reaction of the antigen-antibody type, and

detecting any product formed in a reaction of the antigen-antibody type.

30. (Twice Amended) Kits for application of a method of identification of a bacterium of the species *T. equigenitalis* in a specimen or in a culture, which include:

at least one compound selected from the group consisting of a monoclonal antibody or fragment according to claim 17, an immunogenic protein and a monoclonal anti-antibody or fragment thereof are capable of interacting with said monoclonal antibody or fragment thereof.

reagents, for [carrying out] detecting the intended immunologic reaction, optionally, reagents for blocking the non antigen-antibody reactions, and instructions for use.

35. (Twice Amended) The method according to claim 29, wherein the non antigen-antibody reaction is blocked by saturation of the [collected] specimen [through incubation with] obtained by means of a serum from which [does not contain] anti-*T. equigenitalis* antibodies have been removed.